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EXAMINER	
VAKILI, ZOHREH	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
06/19/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/538,277	SOTO PEREDO, CLAUDIA ANGELICA	
	Examiner	Art Unit	
	Zohreh Vakili	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,10-16 and 19-26* is/are pending in the application.

4a) Of the above claim(s) *1-6 and 10-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/10/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-6, 10-16, 19-26 are presented for examination.

Applicant's response to the restriction requirement filed on March 5, 2007 is acknowledged. Accordingly, Applicant elects Group II (claims 7-9 and 17-18), directed to a for treating diabetes without traverse. Applicant has cancelled claims 7-9, 17, and 18 and requests examination of newly added claims 19-26. Claims 1-6, 10-16 are withdrawn from consideration as being directed to non-elected subject matter. Claims 19-26 read on the elected invention and are herein examined on the merits.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

For the basis of examination the claims are interpreted to read upon a method.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 19-26 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 19-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bibbs et al. (U.S. Pub. No. 2004/0006128), in view of Soto et al. (Comp. Biochem. Physiol. Vol. 119C, No. 2, p. 125-129, 1998, Cited on IDS), and further in view of Coote et al. (U.S. Pub. No. 2004/0167034 A1).

Bibbs et al. teach methods of treating a mammal with high blood-glucose, or high blood-cholesterol and pharmaceutical compositions comprising the same are disclosed

(see abstract). Diabetes mellitus is a chronic condition characterized by the inability to regulate blood glucose levels. Diabetes mellitus is a metabolic disorder of the human body primarily involving an inability of the body to properly store and utilize sugar and other chemical compounds in the metabolism of the body. It is characterized by an elevation in the concentration of sugar in the blood and also by the appearance of sugar in the urine (see page 1, paragraph 0005). Diabetes mellitus is classified into two types, namely, Type I and Type II. In Type I diabetes, the beta cells in the pancreas, probably through an auto-immune reaction, cease production and secretion of insulin into the bloodstream. Insulin is a hormone that is normally secreted into the bloodstream by beta cells within the pancreas. Insulin enables the body to properly utilize and store (as fat) the sugars that enter the bloodstream as part of the digestive process (see page 1, paragraph 0006). In Type I and Type II diabetes, the pancreas continues to produce insulin but some or all of the insulin may fail to bind to the body's cell receptors and/or internalization of insulin in the cells is reduced. In such cases, there may be a sufficient level of insulin in the blood, but the ability of the cells to uptake glucose is reduced (see page 1, paragraph 0008). Bibbs et al. disclose a method of treating a mammal with high blood glucose (see page 1, paragraph 0009). The administered composition comprises less than 40% of other naturally occurring bioflavanoids, while in other embodiments, the composition comprises less than 35% of other naturally occurring bioflavanoids. In yet other embodiments, the composition comprises less than 30%, less than 25%, less than 20%, less than 15%, or less than 10% of other naturally occurring bioflavanoids. In certain embodiments, the

composition comprises less than 5% of other naturally occurring bioflavanoids (see page 1, paragraph 0015). The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes (see page 4, paragraph 60). For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by mixing one or more solid excipient with one or more compound of the invention, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethyl cellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate (see page 4, paragraph 63). Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene

glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses (see page 4, paragraph 64). Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration (see page 4, paragraph 65). For buccal administration, the compositions may take the form of tablets or lozenges (see page 4, paragraph 0066).

Soto et al. teach silymarin a flavonoid extracted from the milk thistle Silybum marianum. This compound has shown protective effects against the oxidative peroxidation of cells. Silymarin functioned as a free radical scavenger, increasing available GSH and preventing membrane alterations. The evidence seems to indicate that diabetes mellitus and its sequels are conditions in which free radicals are involved both in human beings and in experimental models. Alloxan administration causes severe necrosis of pancreatic beta cells. Given these hypotheses, the above model was considered adequate for the study of a pathology in which free radicals might have

a central role, such as diabetes mellitus. The aim of this study was to evaluate the effect of the antioxidant silymarin on the alloxan-induced diabetes mellitus, since its potential protective effects have been previously addressed in other models of cell damage induced by drugs (see page 125, introduction). The main finding of this study was that silymarin prevented a rise in both plasma glucose and pancreatic lipid peroxidation induced by alloxan in rats. This result suggests a protective effect of silymarin against alloxan action. These observations of the effect of silymarin in the area of hepatocyte protection may contribute to explaining why this compound has a protective effect on pancreatic lipid peroxidation with the recovery of the beta cell function. This, in turn, may contribute to the regulation of plasma glucose. It has been suggested that thiol groups are important in the intracellular and membranal redox state of the secretory function of beta pancreatic cells. Silymarin induced an increase in pancreatic glutathione content which may enhance the GSH/GSSG ratio and therefore improve plasma glucose regulation. This study suggests that the induction of diabetes mellitus by alloxan in rats may be prevented by silymarin administration. This drug had a favorable effect on the pancreatic damage produced by the production of free radicals. This is the case in the experimental model of diabetes mellitus induced by alloxan and is probably the case in human diabetes mellitus type I (see page 128 & 129, Discussion).

Coote et al. teach of a process of preparing an emulsion, a composition comprising the emulsion to be administered to human or animal (see page 1, paragraph 0001). Flavonoids phytosterols, carotenoids, and other phytochemicals are

classes of compounds isolated from plants with recognized pharmacological properties. Flavonoids demonstrate free radical scavenging properties (see page 1, paragraph 0003). Coote et al. further disclose liquid dosage forms for oral administration may include pharmaceutically acceptable (or veterinarilly acceptable where the dosage form is intended for animals) in the case of acceptable emulsions, syrups, solutions, suspensions, and elixirs containing inert diluents commonly used in the art, such as water (see page 5, paragraph 0060). A preferred thickening agent is carbopol or equivalent thickening agents (see page 5, paragraph 0061). Solid dosage forms for oral administration may include capsules. In such forms, the emulsion may be admixed with at least one inert diluent such as silicas, dicalcium phosphate, sugars, talcs. In the case of capsules, the dosage forms may also comprise buffering agents. The capsules can additionally be prepared with enteric coatings (see page 5, paragraph 0062). The processes of the present invention are applicable to synthetic drugs, plant and animal compounds plant flavonoids which comprises various subclasses such as flavans, flavanones, flavones, anthocyanins etc. Flavonoids may be monomeric, dimeric, oligomeric and may also exist in free or glycosidic forms phytoestrogens. Flavanolignans from silymarin, and animal compounds such as glucosamine and chondroitin sulphate and hydrophobic synthetic drugs, natural compounds from plants and animals such as carotenoids, lycopene, lutein, tocopherols, phytosterols and waxes such as policosanols (see page 5, paragraph 0067). 50 g water, 300 mg glucosamine hydrochloride and 2 g chondroitin sulphate were mixed. To this was added 2 g excipient (thickening agent, eg.

Carbopol) (see page 7, paragraph 0095). Formulation for 100 g of gel: Complex preparation (as in Examples 1-10). 50 g Triethanolamine 1 g Carboxyvinyl polymer (carbopol 934^{R}) 1.5 g Perfume 0.1 g Sodium hydroxybenzoate 0.2 g Isopropylmyristate 1.0 g d-limonene 0.5 g Distilled water qs to 100 g (see page 8, paragraph 0096). Hepatic formulation consisted of the following: 16.67 kg silymarin (70:1), 6.67 kg Bupleurum falcatum (5:1) and 6.67 kg Schisandra chinensis (16:1). This mixture was then added to 45.67 kg of phytosterol base and tabletised (see page 9, paragraph 0143).

One of ordinary skill in the art would combine the teachings of Bibbs et al. in view of Soto et al., and further in view of Coote et al. Bibbs et al. disclose a composition for lowering blood glucose level. The administered composition comprises less than 10% flavanoids. The pharmaceutical composition for oral administration is formulated as tablets, pills, and suspension and for suitable coating carbopol gel is used. The composition is to treat diabetes mellitus. In Type I diabetes, the beta cells in the pancreas cease production and secretion of insulin into the bloodstream. Soto et al. uses silymarin a flavonoid that functions as a free radical scavenger to a patient with diabetes mellitus induced with alloxan that causes severe necrosis of pancreatic beta cells. Silymarin has shown protective effects of cell damage induced by drugs. Coote et al. disclose pharmaceutical formulations for oral administration such as oral suspension where the flavonoid silymarin is used in different concentrations and in one composition carbopol is used in 2 grams and in another 1.5 grams.

It would have been obvious to a person skilled in the art to employ the teachings

of Bibbs et al. in view of Soto et al., and further in view of Coote et al. considering that such references teach all the components of the claimed invention in a pharmaceutical formulation. The optimal dosage amounts would have been obvious to the skilled artisan. The determination of a dosage of the active ingredient are well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the drug while minimizing adverse or unwanted side effects or even undesirable stability issues. Thus, one of ordinary skill in the art would have been motivated to combine the teachings of the above references and as combined teach the invention as claimed.

One skilled in the art would have been motivated to employ the teachings of Bibbs et al. in view of Soto et al., and further in view of Coote et al. The above references make clear that the claimed components have been previously used in a biological pharmaceutical composition. As combined, the references would have resulted in the claimed invention. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, prima facie obvious over the cited arts.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zohreh Vakili whose telephone number is 571-272-3099. The examiner can normally be reached on 8:30-5:00 Mon.-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Zohreh Vakili

Patent Examiner 1614 May 25, 2007

07 JUNE 2007

Ardin H Marschel 6/9/07
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER